Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

SARS-CoV-2 infection and red blood cells: Implications for long term symptoms during exercise

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Skeletal muscle blood flow is coupled with the oxygenation state of hemoglobin, whereby the red blood cell (RBC) functions as an oxygen sensor and releases adenosine triphosphate (ATP) during deoxygenation to evoke vasodilation, an increase in blood flow and O_2 delivery to tissues, presumably acting on endothelial cell purinergic receptors.[1] A signal transduction pathway relating deoxygenation to ATP release has been described and includes band 3, the most abundant membrane protein in mature RBCs, the heterotrimeric G protein Gi and adenylyl cyclase (AC).[2] In this cell, during hypoxia, Gi activation results in increased cyclic adenosine monophosphate (cAMP) and, ultimately, ATP release following the binding of deoxy-Hb to band 3. Whether this function is impaired in patients with Coronavirus disease 2019 (COVID-19) is unknown. Recent elegant studies by Thomas et al.,[3] and Cosic et al.[4] have shown how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect RBC, hypothesizing new mechanisms to clarify the COVID-19 pathophysiology. According to their hypothesis, membrane RBC is damaged following SARS-CoV-2 infection, in particular, the oxidation process of band 3^3 and binding with S1 spike proteins from SARS-CoV-2.[4] Alterations to band 3 can lead to significant alterations to the RBC functions, such as ATP release mechanism. In this case, hypoxia seen in severe COVID-19 cases is related to SARS-CoV-2-mediated band 3 alteration, which may decrease the ability of RBC to release ATP, reducing vasodilation and oxygen (O_2) delivery to tissues. Interestingly, the role of adenosine in adaptive mechanisms has also been implicated in the field of exercise training.[5] Exercise affects the purinergic system in RBCs and platelets. In particular, increases in ATP and associated metabolites in blood plasma following exercise have been related to the ability of RBC to release ATP in areas of low oxygen tension.[6] Because the average life span of these cells is 100–120 days, damaged RBC from COVID-19 patients may persist in circulation up to three months before being eliminated and replaced. Evaluating targeted exercise interventions and the levels of ATP in plasma would provide insight into the COVID-19 recovery process in patients recovering from SARS-CoV-2 infection, but having persistent symptoms, such as fatigue.[7] These results would provide an understanding of the mechanisms responsible for long term symptoms occurring in patients up to three months after virus infection. Furthermore, a better understanding of the progression of COVID-19 pathology is achieved by observing changes in the morphology and structure of RBC in COVID-19 patients. More experimental data are needed to confirm this hypothesis. Future investigations are warranted regarding how pharmacological treatments can rescue the impaired ATP release from RBC and normalize tissue perfusion in patients with COVID-19.

List of abbreviations

ATP	Adenosine triphosphate
O_2	Oxygen
cAMP	Cyclic adenosine monophosphate
COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Submission statement

This manuscript has not been published and is not under consideration for publication elsewhere.

Conflict of interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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